

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings of claims in the application:

**Listing of Claims:**

1-5. (Canceled)

6. (Currently amended) A method to determine risk of cancer recurrence in a human subject having ER+ (estrogen receptor positive) breast cancer, said method comprising determining an expected cancer recurrence for said human subject by assaying producing cDNA copies of RNA from a sample of breast cancer cells from said human subject ~~[[for]]~~ and determining, based on said cDNA copies, a ratio of HoxB13 and IL17BR RNA expression levels that is higher than the mean (average) ratio of HoxB13 and IL17BR RNA expression levels in ER+ breast cancer cells; or

determining an expected lack of cancer recurrence for said human subject by assaying producing cDNA copies of RNA from a sample of breast cancer cells from said human subject ~~[[for]]~~ and determining, based on said cDNA copies, a ratio of HoxB13 and IL17BR RNA expression levels that is below the mean (average) ratio of HoxB13 and IL17BR RNA expression levels in ER+ breast cancer cells;

wherein said mean (average) ratio of HoxB13 and IL17BR RNA expression levels is determined from the mean (average) of HoxB13 RNA expression levels; levels and the mean (average) of IL17BR RNA expression levels; levels in ER+ breast cancer cell samples from human breast cancer subjects that respond to treatment with an antiestrogen agent against breast cancer and human breast cancer subjects that do not respond to treatment with said antiestrogen agent.

7. (Currently amended) The method of claim 6 wherein said RNA expression level(s) are indicative of the probability of recurrence of cancer via metastasis ~~or of survival outcome.~~

8. (Original)                      The method of claim 6 wherein said antiestrogen agent against breast cancer is selected from a selective estrogen receptor modulator (SERM), selective estrogen receptor downregulator (SERD), or aromatase inhibitor (AI).

9. (canceled)

10. (Currently amended)                      The method of claim 6 wherein said ~~assaying for the expression levels~~ cDNA copies of HoxB13 and IL17BR RNA ~~comprises mRNA~~ are used for RNA amplification from said sample of breast cancer cells.

11. (Currently amended)                      The method of claim 6 wherein said ~~assaying for the expression levels~~ cDNA copies of HoxB13 and IL17BR RNA ~~comprises~~ are used in quantitative polymerase chain reaction (PCR).

12. (Currently amended)                      The method of claim 11 wherein said ~~assaying~~ quantitative PCR is comprises real-time PCR and said ratio of HoxB13 and IL17BR RNA expression levels is expressed as a  $\Delta C_t$  of the  $C_t$  values for HoxB13 and IL17BR RNA expression levels.

13. (Previously presented)                      The method of claim 6 wherein said sample is a formalin fixed paraffin embedded (FFPE) sample.

14. (Currently amended)                      A method to determine outcome of a human subject having ER+ (estrogen receptor positive) breast cancer if treated with an antiestrogen agent against breast cancer, or of a human subject afflicted with breast cancer and treated with an antiestrogen agent against breast cancer, said method comprising:

assaying producing cDNA copies of RNA from a sample of breast cancer cells from said human subject, wherein

a ratio of HoxB13 and IL17BR RNA expression levels, based on said cDNA copies, that is below the mean (average) ratio of HoxB13 and IL17BR RNA expression levels in ER+ breast cancer cells indicates a cancer-free outcome, and

a ratio above the mean (average) ratio of HoxB13 and IL17BR RNA expression levels, based on said cDNA copies, in ER+ breast cancer cells indicates an outcome comprising cancer recurrence;

wherein said mean (average) ratio of HoxB13 and IL17BR RNA expression levels is determined from the mean (average) of HoxB13 RNA expression ~~levels~~, levels and the mean (average) of IL17BR RNA expression ~~levels~~, levels in ER+ breast cancer cell samples from human breast cancer subjects that respond to treatment with said antiestrogen agent against breast cancer and human breast cancer subjects that do not respond to treatment with said antiestrogen agent.

15. (Currently amended)                      The method of claim 14 wherein said RNA expression level(s) are indicative of the probability of recurrence of cancer via metastasis or of survival outcome.

16. (Original)                                      The method of claim 14 wherein said antiestrogen agent against breast cancer is selected from a selective estrogen receptor modulator (SERM), selective estrogen receptor downregulator (SERD), or aromatase inhibitor (AI).

17. (canceled)

18. (Currently amended)                      The method of claim 14 wherein said ~~assaying for the expression levels~~ cDNA copies of HoxB13 and IL17BR RNA ~~comprises mRNA~~ are used for RNA amplification from said sample of breast cancer cells.

19. (Currently amended)                      The method of claim 14 wherein said ~~assaying for the expression levels~~ cDNA copies of HoxB13 and IL17BR RNA ~~comprises~~ are used in quantitative PCR.

20. (Currently amended)                      The method of claim 19 wherein said ~~assaying~~ quantitative PCR is real-time PCR and said ratio of HoxB13 and IL17BR RNA expression levels is expressed as a  $\Delta C_t$  of the  $C_t$  values for HoxB13 and IL17BR RNA expression levels.

21. (Previously presented)                      The method of claim 14 wherein said sample is a formalin fixed paraffin embedded (FFPE) sample.

22. (Original)                      The method of claim 14 wherein said sample is obtained by a minimally invasive technique or selected from core biopsy, excisional biopsy, a ductal lavage sample, a fine needle aspiration sample, or cells microdissected from said sample.

23. (Currently amended)                      A method to [[to]] predict an expected response or lack of response to treatment with an antiestrogen agent against breast cancer in a human ER+ (estrogen receptor positive) breast cancer patient, said method comprising

determining an expected ~~non~~-response to treatment with an antiestrogen agent against breast cancer for said patient by ~~assaying producing cDNA copies of mRNA from~~ a sample of breast cancer cells from said patient [[for]] ~~and determining, based on said cDNA copies,~~ a ratio of HoxB13 and IL17BR RNA expression levels that is higher than the mean (average) ratio of HoxB13 and IL17BR RNA expression in ER+ breast cancer cells; and/or

determining an expected ~~response non-response~~ to treatment with said antiestrogen agent against breast cancer for said patient by ~~assaying producing cDNA copies of mRNA from~~ a sample of breast cancer cells from said patient [[for]] ~~and determining, based on said cDNA copies,~~ a ratio of HoxB13 and IL17BR RNA expression levels that is lower than the mean (average) ratio of HoxB13 and IL17BR expression in ER+ breast cancer cells

wherein said mean (average) ratio of HoxB13 and IL17BR RNA expression levels is determined from the mean (average) of HoxB13 RNA expression ~~levels, levels~~ and the mean (average) of IL17BR RNA expression ~~levels, levels~~ in ER+ breast cancer cell samples from human breast cancer subjects that respond to treatment with said antiestrogen agent against breast cancer and human breast cancer subjects that do not respond to treatment with said antiestrogen agent.

24. (Currently amended)                      The method of claim 23 wherein said RNA expression level(s) are indicative of the probability of recurrence of cancer via metastasis or of survival outcome.

25. (Original)                      The method of claim 24 wherein said antiestrogen agent against breast cancer is selected from a selective estrogen receptor modulator (SERM), selective estrogen receptor downregulator (SERD), or aromatase inhibitor (AI).

26. (canceled)

27. (Currently amended) The method of claim 24 wherein said ~~assaying for the expression levels~~ cDNA copies of HoxB13 and IL17BR RNA ~~comprises mRNA are used for RNA~~ amplification from said sample of breast cancer cells.

28. (Currently amended) The method of claim 24 wherein said ~~assaying for the expression levels~~ cDNA copies of HoxB13 and IL17BR RNA ~~comprises~~ are used in quantitative PCR.

29. (Currently amended) The method of claim 28 wherein said ~~assaying~~ quantitative PCR is real-time PCR and said ratio of HoxB13 and IL17BR RNA expression levels is expressed as a  $\Delta C_t$  of the  $C_t$  values for HoxB13 and IL17BR RNA expression levels.

30. (Previously presented) The method of claim 24 wherein said sample is a formalin fixed paraffin embedded (FFPE) sample.

31. (Original) The method of claim 24 wherein said sample is obtained by a minimally invasive technique or selected from core biopsy, excisional biopsy, a ductal lavage sample, a fine needle aspiration sample, or cells microdissected from said sample.

32. (Currently amended) A method to determine risk of cancer recurrence in a human subject having ER+ (estrogen receptor positive) breast cancer if treated with an antiestrogen agent against breast cancer, said method comprising  
assaying producing cDNA copies of mRNA from a sample of breast cells from said human subject to determine an expected cancer recurrence for said human subject based on an increased expression of HoxB13 sequences, or decreased expression of IL17BR sequences, relative to the mean (average) expression thereof in ER+ breast cancer cell samples from human breast cancer subjects that respond to treatment with said antiestrogen agent and human breast cancer subjects that do not respond to treatment with said antiestrogen agent, as an indicator of non-responsiveness to said antiestrogen agent; or  
to determine an expected lack of cancer recurrence for said human subject based on a decreased expression of human HOXB13 sequences, or increased expression of IL17BR sequences, relative to the mean (average) expression thereof in ER+ breast cancer cell samples from human breast cancer subjects that respond to treatment with said antiestrogen agent and human breast cancer subjects

that do not respond to treatment with said antiestrogen agent, as an indicator of responsiveness to said antiestrogen agent.

33. (Original)                      The method of claim 32 wherein said antiestrogen agent against breast cancer is selected from a selective estrogen receptor modulator (SERM), selective estrogen receptor downregulator (SERD), or aromatase inhibitor (AI).

34. (Previously presented)                      The method of claim 32 wherein said sample of breast cancer cells is ER+ or is obtained by a minimally invasive technique or selected from core biopsy, excisional biopsy, a ductal lavage sample, a fine needle aspiration sample, or cells microdissected from said sample.

35. (Currently amended)                      The method of claim 32 wherein said ~~assaying~~ for cDNA copies of HoxB13 and/or IL17BR RNA are used for RNA sequence expression ~~comprises HoxB13 and/or IL17BR mRNA~~ amplification from said sample of breast cancer cells.

36. (Currently amended)                      The method of claim 32 wherein said ~~assaying~~ comprises cDNA copies are used in quantitative PCR.

37. (Previously presented)                      The method of claim 32 wherein said sample is a formalin fixed paraffin embedded (FFPE) sample.

38. (Currently amended)                      The method of claim 32 wherein said assaying is by hybridization to a polynucleotide comprising sequences of at least 15 nucleotides from the 3' untranslated region, the coding region, or the 5' untranslated ~~region, region~~ of human HoxB13 and/or IL17BR sequences.

39-41. (canceled)

42. (Currently amended)                      The method of ~~claim 35~~ claim 36 wherein said ~~assaying~~ comprises quantitative PCR is real-time PCR and said ratio of HoxB13 and IL17BR RNA expression levels is expressed as a  $\Delta C_t$  of the  $C_t$  values for HoxB13 and IL17BR RNA expression levels.

43-48. (canceled)

49. (Previously presented)      The method of claim 6 wherein said assaying comprises detecting expression of an IL17BR sequence selected from SEQ ID NOS: 1, 2, 3, or 8, or 32-34.

50. (Previously presented)      The method of claim 6 wherein said assaying comprises detecting expression of a HoxB13 sequence selected from SEQ ID NOS: 6, 7, 10, 11-31, 35 or 37.

51. (canceled)

52. (Previously presented)      The method of claim 14 wherein said assaying comprises detecting expression of a HoxB13 sequence selected from SEQ ID NOS: 6, 7, 10, 11-31, 35 or 37.

53. (Previously presented)      The method of claim 14 wherein said assaying comprises detecting expression of an IL17BR sequence selected from SEQ ID NOS: 1, 2, 3, or 8, or 32-34.

54. (Previously presented)      The method of claim 23 wherein said assaying comprises detecting expression of a HoxB13 sequence selected from SEQ ID NOS: 6, 7, 10, 11-31, 35 or 37.

55. (Previously presented)      The method of claim 23 wherein said assaying comprises detecting expression of an IL17BR sequence selected from SEQ ID NOS: 1, 2, 3, or 8, or 32-34.

56. (Previously presented)      The method of claim 32 wherein said assaying comprises detecting expression of a HoxB13 sequence selected from SEQ ID NOS: 6, 7, 10, 11-31, 35 or 37.

57. (Previously presented)      The method of claim 32 wherein said assaying comprises detecting expression of an IL17BR sequence selected from SEQ ID NOS: 1, 2, 3, or 8, or 32-34.

58. (Previously presented)      The method of claim 6 wherein said sample is obtained by a minimally invasive technique or selected from core biopsy, excisional biopsy, a ductal lavage sample, a fine needle aspiration sample, or cells microdissected from said sample.

59. (Previously presented)      The method of claim 32 wherein said expression level(s) are indicative of the probability of recurrence of cancer via metastasis or survival outcome.

60. (Previously presented)      The method of claim 32 wherein said assaying comprises determining the expression levels of HoxB13 and/or IL17BR mRNAs.

61. (Currently amended)      The method of claim 6 wherein said assaying is by hybridization to a polynucleotide comprising sequences of at least 15 nucleotides from the 3' untranslated region, the coding region, or the 5' untranslated ~~region~~, region of human HoxB13 or IL17BR sequences.

62. (Currently amended)      The method of claim 14 wherein said assaying is by hybridization to a polynucleotide comprising sequences of at least 15 nucleotides from the 3' untranslated region, the coding region, or the 5' untranslated ~~region~~, region of human HoxB13 or IL17BR sequences.

63. (Currently amended)      The method of claim 23 wherein said assaying is by hybridization to a polynucleotide comprising sequences of at least 15 nucleotides from the 3' untranslated region, the coding region, or the 5' untranslated ~~region~~, region of human HoxB13 or IL17BR sequences.

64-66. (canceled)

67. (New)      The method of claim 12 wherein said antiestrogen agent is tamoxifen.

68. (New)      The method of claim 20 wherein said antiestrogen agent is tamoxifen.

69. (New)      The method of claim 29 wherein said antiestrogen agent is tamoxifen.

70. (New)      The method of claim 42 wherein said antiestrogen agent is tamoxifen.



### **REMARKS/ARGUMENTS**

As discussed further below, the claims have been revised to use alternative language to encompass the intended subject matter and to correct minor informalities without alteration in claim scope.

No new matter has been introduced, and entry of the above amendments is respectfully requested.

#### **Priority**

Applicants acknowledge, but disagree with, the statements on pages 3-4 of the Office Action. Applicants respectfully submit that there has not been sufficient consideration provided to the descriptive support present in the priority document. But given the absence of any rejections based upon cited documents, Applicants believe that no further discussion of this issue is necessary.

#### **Claim objections**

Claim 7 was objected to as being of improper dependent form. Applicants have revised the claim to obviate this objection.

Claims 9, 17, and 26 were objected to for failing to further limit Claims 6, 14, and 23, respectively. Applicants have canceled Claims 9, 17 and 26 to obviate this objection.

Claims 6, 14 and 32 were objected to for the presence of certain informalities, with suggestions of alternative language provided by the Office. Applicants thank the Office for the suggestion and have revised the claim to obviate the objection. Applicants point out, however, that the suggestion to introduce “the” into the preamble appears unnecessary.

Claims 7, 15, 23, 38, and 61-63 were objected to for the presence of certain informalities, with suggestions of alternative language provided by the Office. Applicants thank the Office for the suggestion and have revised the claim to obviate the objection.